

REMARKS/ARGUMENTS

Claims 1, 2 and 5-20 are active in this application.

As set forth in independent Claim 1, the invention is directed to a process for preparing macrocyclic ketones of formula I where X comprises a C₁₀-C₁₇ alkyl radical. This reaction takes place in a gas phase in a manner where the compound of Formula 2 is evaporated and then passed at a desired reaction temperature in gaseous form over the catalyst arranged in a fixed bed.

This claim process is not obvious in view of the combination of Decker (U.S. Patent No. 4,745,228) and Ruzika (U.S. Patent No. 1,702,843) because there would not have been motivation to combine the two references nor a reasonable expectation of success on the order observed by the Applicants even if one were to do so.

As noted by the Office, Decker describes the preparation of cyclic C₅ to C₇ ketones only, in other words much smaller cyclic ketones than that being claimed. Notwithstanding this deficiency, the Office then cites the Ruzika patent which describes the preparation of larger cyclic ketones.

First, as been noted previously, the Ruzika patent requires that the reaction takes place in a condensed phase and not a gas phase as claimed because the corresponding titanium salt as formed in the Ruzika reaction are not volatile at the reaction temperature and must take place in the condensed phase otherwise no reaction would occur. This clearly teaches away from performing the reaction of the Ruzika material in another manner such as a gas or liquid phase as taught by Decker.

Moreover, based on what is known from studying the reaction in Ruzika cyclization of larger ketones (as in Ruzika and the claims) yields are on the order of 5% or less (see the attached Organic Chemistry textbook from Fieser and Fieser, 3rd Edition, 1956 at page 318,

last paragraph referencing the Ruzika reaction; see also the attached publication by Renz at *Eur J Org Chem* 2005, 979-988; page 986, first column).

Therefore, one would have no motivation to combine the teachings of the two references with a reasonable expectation of success.

Contrary to this conventional wisdom in the field, the Inventors here have discovered that one can prepare cyclic ketones with C10-C17 in a gas phase over a heterogenous catalyst at quite significant yields of 45 and 78% of the product (see Examples 1 and 2 on page 5 of the application. Surely, these types of yields could not have been expected on the basis of what was previously known to be the yields of preparing cyclic ketones as claimed.

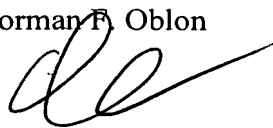
Still further, as discussed in the specification on page 3 an advantage of the process according to the invention is that the cyclization, saponification and subsequent decarboxylation steps which are normally customary in a Dieckmann condensation carried out in solution take place in a single step in the gas phase, without isolation of the respective intermediates. A further advantage is that less solvent is required, which leads to a cost advantage and a reduced amount of waste which may have to be worked up.

In view of the above comments, Applicants request reconsideration and withdrawal of the rejection based on the combination of Decker and Ruzika.

Applicants also request allowance of all pending claims.

Respectfully submitted,

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Ketonization of Carboxylic Acids by Decarboxylation: Mechanism and Scope

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Keywords: Carboxylic acids / Catalysis / Decarboxylation / Ketones

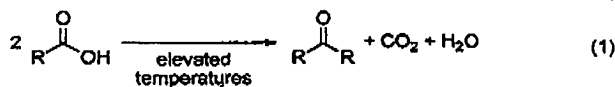
In the ketonic decarboxylation process, a ketone is formed from two moles of carboxylic acid; water and carbon dioxide are produced as side-products. At present, the mechanism of this reaction remains under debate; it has been proposed as a radical mechanism, a mechanism involving a β -keto acid as intermediate, or a concerted mechanism. This paper demonstrates that the latter mechanism is the most likely one and that weak bases may play the role of promoters. Different

processes are reviewed for the syntheses of the following ketones: symmetrical ketones, such as acetone or 3-pentanone, cyclic ketones, such as cyclopentanone (parent compound and substituted derivatives), fatty ketones, and some unsymmetrical ketones.

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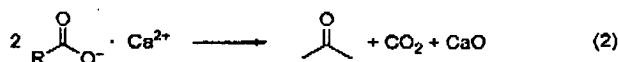
Introduction

The ketonization of carboxylic acids by decarboxylation, also called ketonic decarboxylation, is useful synthetically for the production of symmetrical ketones such as acetone, 3-pentanone, cyclopentanone, and fatty ketones. When starting with two different carboxylic acids, the process leads to a mixture of three products, namely the two corresponding symmetrical ketones together with the "mixed" ketone. In the ketonic decarboxylation, two carboxylic acid functionalities are converted into a carbonyl group, carbon dioxide, and water [Equation (1)]. From the modern, ecological point of view, this process is a very clean one because non-polluting by-products are formed and no solvent or other elaborate reagent is necessary.



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As a result, this reaction is an interesting one for potential industrial applications, even though it is one of the oldest reactions known in organic chemistry. The dry distillation of calcium acetate to yield acetone was reported as early as 1858^[1] [Equation (2)]; until World War I, this reaction was employed for the commercial manufacture of acetone.^[2]



In an improved procedure, which involves dry distillation passing superheated steam at a temperature of about 300–400 °C, acetone can be obtained in 95% yield.^[3] Very early on, the ketonic decarboxylation was performed using carboxylic acids and less-than-stoichiometric amounts of base to form a mixture of the free carboxylic acid and its metal salt. For instance, adipic acid was reacted with 4 mol-% of barium hydroxide, 4 mol-% of uranium nitrate, or 4 mol-% of iron sulfate at 290–295 °C to give cyclopentanone almost quantitatively.^[4] These changes were not introduced by the



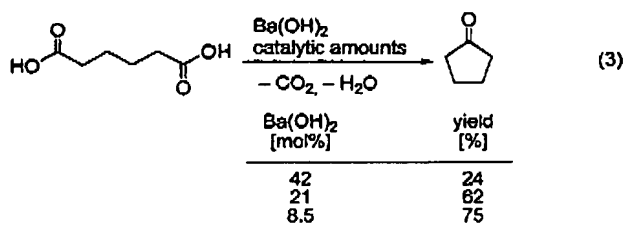
Michael Renz was born in 1969 in Erlenbach am Main, Germany. He obtained his Ph. D. under the supervision of Professor Waldemar Adam (Würzburg, Germany) and Professor Avelino Corma (Valencia, Spain) in 1997. Then he moved to the "Laboratoire de Chimie de Coordination du CNRS" (Toulouse, France) for a post-doctorate with Professor Bernard Meunier. In 1999 he returned to the Institute of Chemical Technology, Valencia, for a post-doctoral stay with Avelino Corma. At the same research centre, he received a "Ramón & Cajal" fellowship from the Spanish Government, starting in 2002. His current research interest is the catalysis of organic reactions of industrial interest, especially using solid Lewis acids.

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forces of ecological considerations or requirements but rather by the fact that better yields were achieved this way. It has been demonstrated elegantly that in the synthesis of cyclopentanone from adipic acid in the presence of barium hydroxide, 75% of the ketone can be obtained when using only 8.5 mol-% of the base [Equation (3)], whereas the yield dropped to 25% when 42 mol-% of barium hydroxide was used.^[5] Furthermore, and fulfilling even the requirements of the modern processes of recycling and waste reduction, a semi-continuous procedure was developed in 1928 after it was realized that the baryta residue of the dry distillation could be re-used, rather than adding fresh base, together with fresh charges of adipic acid.^[5]



At around the same time, real catalytic processes were reported in the gas phase using heterogeneous catalysts, e.g., passing adipic acid vapours over manganese(II) oxide at 350 °C gave an 80% yield of cyclopentanone.^[6] Furthermore, in a sufficiently slow distillation, cyclopentanone also can be produced from adipic acid without the need for any additive, merely by placing it in a laboratory glass (60% yield)^[7,8] or quartz (95% yield)^[8] flask.

The many different early versions of the reaction – i.e., the great diversity of promoting materials employed in varying amounts and reactions performed in the presence of water or under strictly anhydrous conditions – confused chemists, especially when they began to determine the mechanism.^[8,9] At the time, they were unable to distinguish between ketonic decarboxylation, ketonic decarboxylation under forced reaction conditions involving side reactions,

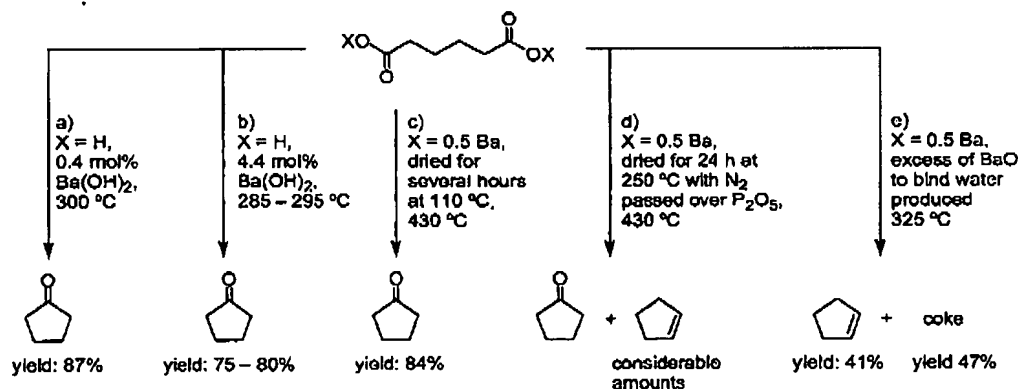
and oxidative decarboxylation. In the following sections, the experimental results are provided from a retrospective point of view in an effort to minimise confusion. An excellent and detailed historical overview can be obtained from the literature.^[9]

The Mechanism and Corresponding Experimental Support

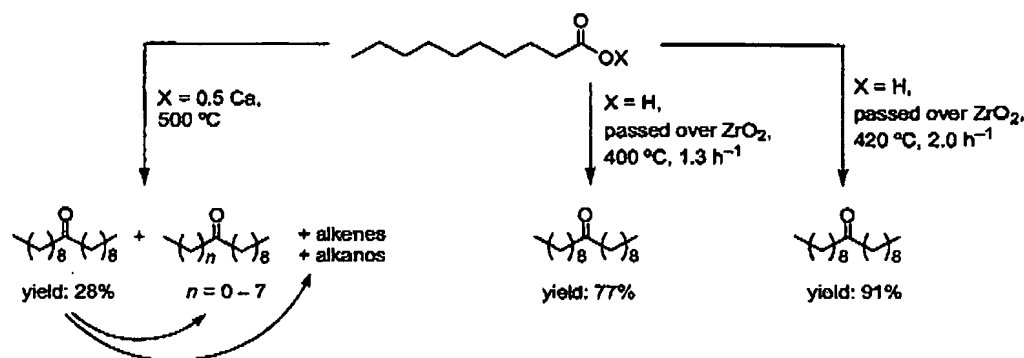
The first problems to be resolved before beginning the elucidation of the mechanism are (a) the choice of reaction conditions that must be considered, (b) which conditions provoke predominantly side reactions, and (c) which products belong to which reaction. In particular, the benefits, the advantages, and the drawbacks of each of the two alternative methods of the ketonic decarboxylation – i.e., reactions using carboxylic acid salts and those using less-than-stoichiometric amounts of base – should be determined. In this regard, a careful literature study suggests, surprisingly, that an unambiguous advantage exists for the catalytic method.

The cyclisation of adipic acid promoted by barium hydroxide is presented here as the first example. As mentioned above, cyclopentanone can be obtained when using barium hydroxide in catalytic amounts: with 4.4 mol-% Ba(OH)₂ at a temperature of 285–295 °C in 75–80% yield^[10] or in the semi-continuous procedure using 0.4 mol-% Ba(OH)₂ at a temperature of ca. 300 °C in 87% yield^[5] (Scheme 1, conditions a and b). In contrast, when the reaction is performed using stoichiometric amounts of barium hydroxide, i.e., with the barium salt of diadipate, and when the salt has been rigorously dried, the ketonisation begins at a significantly higher temperature (430 °C) and, additionally, considerable amounts of cyclopentene are obtained as a by-product (conditions d).^[8]

The presence of water must be avoided in these mechanistic control reactions because its interference increases the possibility that barium adipate will form barium oxide and free adipic acid. Consequently, the reaction can begin to produce increasingly more water, which, for its part, facili-



Scheme 1. Results of the ketonic decarboxylation of adipic acid conducted in the presence of different amounts of barium hydroxide and water

Scheme 2. Ketonic decarboxylation of decanoic acid, as its calcium salt or passed over ZrO_2 .

tates a smooth reaction. Thus, the reaction can be considered to be the ketonic decarboxylation of adipic acid when less-than-stoichiometric amounts of base are used in the presence of an inorganic salt, namely barium oxide or barium carbonate, that is mainly non-interfering. Indeed, when barium diadipate is not rigorously purified from traces of adipic acid or is not dried excessively, the reaction proceeds at 430 °C to result in cyclopentanone in 84% yield (Scheme 1, conditions c).^[8] Furthermore, in the presence of an excess of barium oxide to bind the water that is formed during the reaction, no cyclopentanone product is observed, but cyclopentene (41%) and coke are formed (conditions c).^[8]

The kinetic decarboxylation of adipic acid to cyclopentanone, however, might be an exceptional case because it involves a cyclisation that might be favourable or inopportune for a particular (side) reaction. Therefore, the transformation of decanoic acid to 10-nonadecanone is cited as a further example of intermolecular ketone formation and very similar conclusions are drawn. When decanoic acid is passed over zirconium oxide at 400 °C and at a space velocity of 1.3 h⁻¹, the ketone is obtained in 77% yield (Scheme 2).^[11] Increasing the temperature to 420 °C and the space velocity to 2.0 h⁻¹ improves the yield to 91%.^[11] Again, in contrast, the pyrolysis of calcium decanoate at 500 °C results in a complex product mixture including 10-nonadecanone in a corresponding yield of 28% (Scheme 2).

The remaining material consisted of the series of nonyl-ketones from 2-undecanone to 9-octadecanone and considerable amounts of alkanes and alkenes.^[12] The experimental data from a detailed study of the by-products have been interpreted by the authors in terms of a free radical mechanism, which became quite popular for understanding the ketonic decarboxylation.^[13] However, a more-recent study on the pyrolysis of model compounds over spent oil shale at 500 °C established that 10-nonadecanone was the primary product from decanoic acid. When the acid was passed at high space velocities (residence time = 15 s), 10-nonadecanone was the most abundant product, followed by 2-undecanone (and trace amounts of all other members of the series) and nonane as the most abundant hydrocarbon product.^[14] At a low space velocity (residence time =

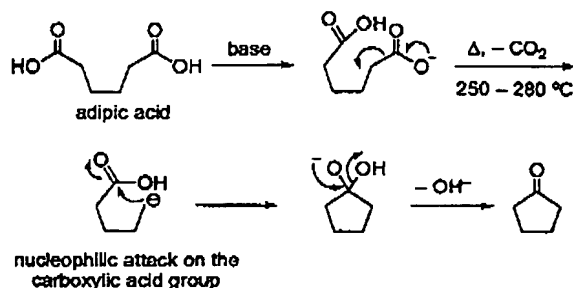
5 min), the composition of the product mixture changed to give 2-undecanone as the most abundant ketone (in the corresponding series) in a mixture together with C₄-C₉-alkanes and alkenes and aromatic hydrocarbons. It has been concluded that, at low residence times, decanoic acid formed the symmetrical ketone, 10-nonadecanone. At high residence times, cracking of the alkyl chain occurred to yield predominately 2-undecanone by a favoured β -homolysis (resonance stabilization).

It is evident from all these experimental data that the ketonic decarboxylation proceeds when using catalytic amounts of base. In the presence of stoichiometric amounts of base, the reaction is prevented, or at least slowed down, and the temperature must be raised to achieve any transformation. Under these conditions (>450 °C), cracking reactions compete efficiently to produce a typical series of undesired by-products. Water can run the blockade, forming (in an equilibrium) free carboxylic acid and free base, especially when metal oxides are formed readily. This observation may explain the early makeshift attempts to employ superheated steam with carboxylates and a selection of counterions, often alkaline earth metal ions.

An interpretation of these conclusions in mechanistic terms was introduced by Rand et al. in 1961, who suggested that one carboxylate functionality reacts with a carboxylic acid functionality.^[13] For the transformation of adipic acid into cyclopentanone in the presence of different amounts of potassium fluoride as base, similar observations as those reported above were again made when the reaction was performed using different amounts of barium hydroxide. The low conversion at stoichiometric amounts of base contrasted the good yield (81%) obtained when using only 5 mol-% of potassium fluoride, although in this case the reaction rate was slower. From these experimental results, Rand et al. proposed a mechanism that begins with the formation of the monocarboxylate of adipic acid (Scheme 3). The elevated temperature serves to decarboxylate the deprotonated acid functionality to form a carbanion that is preferentially cyclised by a nucleophilic attack onto the remaining carboxyl group. The resulting anion eliminates a hydroxide anion to give cyclopentanone. The liberated base can then begin a new reaction cycle.

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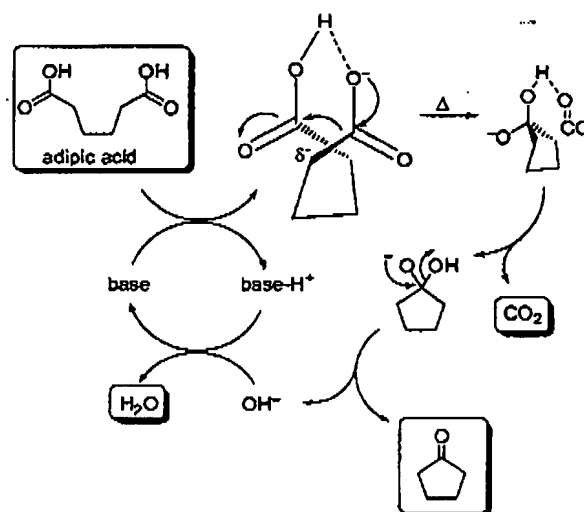
Scheme 3. Mechanism proposed by Rand et al.^[15] for the ketonic decarboxylation of adipic acid to give cyclopentanone; this process involves deprotonation, decarboxylation, and nucleophilic attack on the non-dissociated carboxylic acid group

The key feature of this mechanism is that it provided, for the first time, an explanation for why a stoichiometric amount of base reduces the yield of ketone. With an equimolar amount of base the dicarboxylate is formed and, after the decarboxylation of one of them, the resulting carbanion would have to attack the second carboxyl group in its deprotonated form, which is strongly disfavoured.

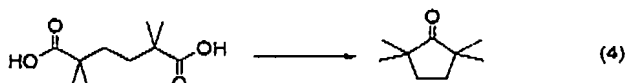
Furthermore, the two negative charges would repel each other and would complicate the approach. Consequently, the transformation does not occur at the same reaction temperature. This proposed mechanism, however, has an inconsistency: the carbanion formed by decarboxylation should be protonated immediately by the carboxylic acid to form pentanoic acid, but this product has never been reported.

An improved version of this proposed mechanism should modify it slightly such that the decarboxylation and nucleophilic attack occur in a concerted fashion, as depicted in Scheme 4. The exact geometry of the transition state might differ from the one depicted – it must be refined by theoretical calculations – as might the extent of negative partial charge at the migrating carbon atom. A concerted reaction mechanism has also been proposed earlier from a study of the fractionation of carbon isotopes in the pyrolysis of barium adipate:^[16] the same isotopic compositions were found in the liberated carbon dioxide, in the cyclopentanone product, and in the starting adipic acid; no enrichment was observed. Consequently, the same number of carbon–carbon and carbon–oxygen bonds must be broken and formed in the rate-determining step. It is straightforward to consider that the deprotonation of the acid is very fast and that the second step is the rate-determining one.

The mechanism proposed in Scheme 4 explains many particularities of the ketonic decarboxylation and is in accordance with a number of experimental observations, e.g., the formation of ketones from carboxylic acids that lack an α -hydrogen atom, such as the cyclisation of 2,2,5,5-tetramethyladipic acid to 2,2,5,5-tetramethylcyclopentanone, which has been achieved using either 15 mol-% of barium oxide or 45 mol-% of potassium fluoride in 72 or 52% yield, respectively [Equation (4)].^[15] This cyclisation cannot be explained by the mechanism involving a β -keto acid intermediate.^[17]

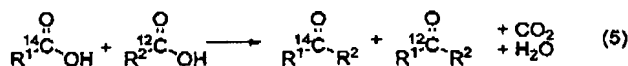


Scheme 4. Modified mechanism involving decarboxylation and nucleophilic attack on the non-dissociated carboxylic acid group in a concerted fashion; the adipic acid substrate is deprotonated by a base to give the monoanion; this carboxylate eliminates carbon dioxide at elevated temperatures and the resulting carbanion simultaneously attacks the second carboxylic acid group to form a deprotonated ketone hydrate; the latter species decomposes into the product ketone and a hydroxide anion, which, for its part, generates a new monoanion, either by direct deprotonation of adipic acid or via regeneration of the catalytic base



Reaction conditions:
15 mol% BaO, 5 h, 320 – 330 °C, yield 72%; or
45 mol% KF, 8 h, 320 – 340 °C, yield 52%

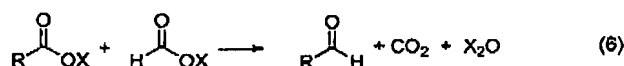
In reactions of compounds containing two different carboxylic acids, the question of which of the carboxylic acid functionalities is transformed into carbon dioxide and which provides the carbonyl functionality in the resulting ketone has been addressed through isotope labelling experiments [Equation (5)]. With two aliphatic carboxylic acids, carbon dioxide is formed preferentially from the carboxylic acid whose alkyl group (formed by a hypothetical decarboxylation) better stabilizes a (partial) negative charge.



This concept is in accordance with the mechanism depicted in Scheme 4 where a carbon atom migrates while bearing a negative partial charge. Examples include the transformation of ¹⁴C-labelled homocamphoric acid into camphor,^[18] the ketonic decarboxylation of the thorium salts of ¹⁴C-labelled isobutyric acid and acetic acid,^[19] the transformation of the calcium salts of valeric acid and ¹⁴C-

labelled acetic acid,^[20,21] and the ketonisation^[19] of the thorium salts of ¹⁴C-labelled phenylacetic acid with the corresponding salt of acetic acid. The only exceptions to this rule are the benzoic acid derivatives, which are more resistant to the decarboxylation than the stabilities of their corresponding anions predict.^[19]

The reaction of a carboxylic acid (salt) with formic acid (salts) would also fit the definition described at the onset for ketonic decarboxylation, although the product in this case is an aldehyde, instead of the ketone, together with carbon dioxide and water [Equation (6)]. However, formic acid is a strong reducing agent^[22] that is employed as a hydride/hydrogen source or precursor, e.g., in the Wallach reaction and in the reduction of nitro compounds to amines,^[23] and can decompose by dehydrogenation in the gas phase.^[24] Therefore, from a mechanistic point of view, it should be considered as an exceptional case and, therefore, it is not included here.



In conclusion, the ketonic decarboxylation can be described as the attack of a carbanion, formed by decarboxylation from a carboxylate, onto a carboxylic group. The decarboxylation and the nucleophilic attack should occur in a concerted fashion. Evidence for the formation of a negative partial charge may be obtained from cross-ketonic decarboxylations using two different carboxylic acids – one of them featuring a labelled carboxylic carbon atom. The decarboxylation predominates in the substrate whose alkyl group best stabilizes a (partial) negative charge. A radical mechanism can be ruled out by comparison with the oxidative decarboxylation.^[25] The mechanism of this related reaction is generally accepted to be of a free radical type, but the product distribution is completely different. Results that have been cited previously in favour of a radical mechanism in the ketonic decarboxylation may be classified as “obtained under forced reaction conditions,” i.e., the by-products were formed by classical cracking reactions that can be avoided by utilising milder conditions. As a consequence of the proposed mechanism and when designing new experiments, it should be noted that the decomposition of metal salts and, equivalently, the use of stoichiometric amounts of base are unfavourable procedures. A catalytic amount of any material that can be protonated by carboxylic acids may be employed as a homogeneous or heterogeneous promoter.^[26] Generally, the ketonic decarboxylation is performed without the use of a solvent; only in a few cases have high-boiling hydrocarbons been used.

Synopsis and Scope of the Ketonic Decarboxylation

The first preparative ketonic decarboxylation was performed in the mid-nineteenth century to provide acetone from calcium acetate. At present, acetone is the most im-

portant commercial ketone, but ketonic decarboxylation is not utilised for its production. Instead, acetone is mainly co-produced in the Hock phenol process; other straightforward syntheses, such as the direct oxidation of propene or the dehydrogenation of 2-propanol, are available. Nevertheless, in recent years acetic acid has been used as a probe molecule for activity tests of catalysts for the ketonic decarboxylation (Table 1),^[27] whereas the decomposition of metal salts has become irrelevant. The preferred reaction protocol is to place a solid catalyst in a continuous reactor and to pass acetic acid vapours over it in a temperature range from 325 to 375 °C. It is clear that zeolite catalysts, which are the most important and most common catalysts used in the chemical industry, are not the most suitable ones for mediating ketonic decarboxylation (Table 1, entry 1). Carboxylic acids placed under severe reaction conditions are readily converted into aromatic hydrocarbons because the primary reaction product, acetone, undergoes a number of condensation and isomerisation reactions.^[28] As a consequence, the selectivity towards acetone is very low. More appropriate catalysts are basic metal oxides, which provide acetone almost quantitatively (Table 1, entries 3 to 8). CeO₂ and MnO₂ on alumina are the most efficient catalysts because almost complete conversion can be achieved at a relatively low temperature (325 °C) and at a quite high weight hourly space velocity (WHSV; Table 1, entries 3 and 4). Other interesting catalytic materials are zirconium oxide (entry 7), optionally modified with sodium oxide (entry 6), or hydrotalcites, which are layered mixed hydroxides of aluminium and magnesium (entry 5).

Table 1. Transformation of acetic acid into acetone through ketonic decarboxylation

Entry	T [°C]	WHSV ^(a) [h ⁻¹]	Catalyst	Conv. [%]	Yield [%]	Select. [%]	Ref.
1	320	0.1	H-ZSM-5	47		22	[28]
2	325	0.34	K ₂ O (10 wt.-%, wet) on Co/MoO ₄	29		38 ^(b)	[29]
3	325	2.1	CeO ₂ (20 wt.-%) on Al ₂ O ₃		93		[30]
4	325	2.1	MnO ₂ (20 wt.-%) on Al ₂ O ₃		96		[30]
5	350	0.57	hydrotalcite Mg/Al = 4	86		high	[31]
6	350	0.37	Na ₂ O (1.3 wt.-%) on ZrO ₂		95		[32]
7	375	0.37	ZrO ₂		99		[33]
8	375	2.1	manganese nodules ^(c)		95		[33]
9	450	0.57	ZnO/Al ₂ O ₃ (3:1) ^(d)	89		high	[34]

[a] Weight hourly space velocity. [b] CO₂ (62%) was detected. [c] Natural mixed oxides involving Mn, Fe, Cu, Ni, Co, Na, K, Ca, Si, and Al. [d] Layered double hydroxides.

The next higher symmetrical homologue of acetone, 3-pentanone, is also of commercial interest. It is used as a solvent for paints and in fragrances and it is a common starting material for organic syntheses. In contrast to acetone, 3-pentanone is produced preferentially by ketonic de-

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carboxylation of the corresponding carboxylic acid: propionic acid.^[35] This situation is evidenced by the number of patents disclosed on this subject. Suitable catalysts for this process are CeO₂ and MnO₂ on alumina, which provide excellent performance with very high conversions and selectivities (Table 2, entries 1, 2, 4, and 11). All oxides of the alkali metals on an anatase support represent active materials, although at a quarter of the WHSV of entries 1 and 2, and provide the desired 3-pentanone almost quantitatively (Table 2, entries 6–10).

Table 2. Transformation of propionic acid into 3-pentanone through ketonic decarboxylation

Entry	T [°C]	WHSV ^[a] [h ⁻¹]	Catalyst	Water ^[b] [wt.-%]	Yield [%]	Ref.
1	325	2.1	CeO ₂ (20 wt.-%) on Al ₂ O ₃		93	[36]
2	325	2.1	MnO ₂ (20 wt.-%) on Al ₂ O ₃		95	[36]
3	330	19	ZrO ₂		95	[36]
4	350	2.1	CeO ₂ (20 wt.-%) on Al ₂ O ₃		92	[37]
5	350	0.6	ZrO ₂		98	[38]
6	360	0.48	Li ₂ O (2 wt.-%) on TiO ₂	10	95	[39]
7	360	0.59	Na ₂ O (2 wt.-%) on TiO ₂	12	99	[39]
8	360	0.50	K ₂ O (2 wt.-%) on TiO ₂	12	99	[39]
9	360	0.59	Rb ₂ O (2 wt.-%) on TiO ₂	12	98	[39]
10	360	0.48	Cs ₂ O (2 wt.-%) on TiO ₂	10	97	[39]
11	375	2.1	MnO ₂ (20 wt.-%) on Al ₂ O ₃		90	[40]
12	425	2.1	manganese nodules		90	[41]

[a] Weight hourly space velocity. [b] Water added to feed. [c] Propionic acid added continuously to high-boiling paraffins.

Higher symmetrical ketone homologues are produced on a smaller scale and are mainly employed as intermediates. Table 3 summarises the formation of 4-heptanone, 2,4-dimethyl-3-pentanone, and 5-nonanone from *n*-butyric, isobutyric, and *n*-pentanoic acids, respectively. The corresponding ketones can be obtained in excellent yield, but the reaction conditions and catalysts must be selected carefully and optimised because side reactions, such as cracking of the alkane chains, may occur.

Table 3. Formation of 4-heptanone, 2,4-dimethyl-3-pentanone, and 5-nonanone through ketonic decarboxylation of the corresponding carboxylic acids

Entry	Carboxylic acid	T [°C]	WHSV ^[a] [h ⁻¹]	Catalyst	Yield [%]	Ref.
1	<i>n</i> -butyric	450	0.46	Al ₂ O ₃	78	[40]
2	isobutyric	350	0.6	ZrO ₂	98	[38]
3	<i>n</i> -pentanoic	400	2.1	MnO ₂ (20 wt.-%) on Al ₂ O ₃	> 88	[37]
4	<i>n</i> -pentanoic	400	2.1	CeO ₂ (20 wt.-%) on Al ₂ O ₃	> 75	[37]
5	<i>n</i> -pentanoic	450	0.46	Al ₂ O ₃	89	[40]

[a] Weight hourly space velocity.

In several cases, ketonic decarboxylation provides a valuable entry point for preparing unsymmetrical ketones, but, in the cross decarboxylations of two different carboxylic acids, the symmetrical ketones are always produced as well. Consequently, the selectivity towards the desired ketone is quite low in the product mixture of the three products because of statistical reasons. Thus, reaction of acetic acid and butanoic acid (Table 4, entry 1) provides 2-pentanone in only 43% yield together with acetone (30%) and 4-heptanone (33%). This disadvantage can be diminished by employing one of the carboxylic acids in excess—either a very cheap one or one that results in a valuable, symmetrical ketone as the co-product. In this manner, several methyl ketones are produced by ketonic decarboxylation employing an excess of acetic acid, which is quite cheap and provides acetone as a by-product that can be commercialised. Thus, reaction of acetic acid and isobutyric acid has resulted in yields of 66 and 72% of methyl isopropyl ketone, based on isobutyric acid (Table 4, entries 2 and 3). Pinacolone was obtained in 81% yield, or in 58% yield at a conversion of 60%, which corresponds to a selectivity of 97% (Table 4, entries 4 and 5). A very interesting product obtained by cross-ketonic decarboxylation is 1-phenylacetone, which is a useful intermediate for the pharmaceutical industry that cannot be formed directly through a simple Friedel–Crafts acylation or alkylation (entry 7). Although this

Table 4. Transformation of carboxylic acids into asymmetric ketones through ketonic decarboxylation

Entry	Acid substrates	Mass ratio ^[b]	T [°C]	WHSV ^[b] [h ⁻¹]	Catalyst	Product	Yield [%]	Ref.
1	acetic, butanoic	37:52:11	430	0.35	ZrO ₂ (10 wt.-%) on TiO ₂	2-pentanone	43	[41]
2	acetic, isobutyric	40:40:20	380	0.47	Na ₂ O (1.3 wt.-%) on TiO ₂	methyl isopropyl ketone	72	[39]
3	acetic, isobutyric	44:44:11	430	0.37	ZrO ₂ (10 wt.-%) on TiO ₂ or ThO ₂ (10 wt.-%) on TiO ₂	methyl isopropyl ketone	66	[41]
4	acetic, pivalic	62:18:20	450	0.84	Na ₂ O (1.3 wt.-%) on TiO ₂	pinacolone	81	[39]
5	acetic, pivalic	40:48:12	435	0.97	Nd ₂ O ₃ (32.5 wt.-%) on Al ₂ O ₃ ^[d]	pinacolone	58 ^[d]	[42]
6	acetic, lauric	69:31:0	430	0.36	ZrO ₂ (10 wt.-%) on TiO ₂	2-tridecanone	60	[41]
7	acetic, phenylacetic	66:30:4	430	0.36	ZrO ₂ (10 wt.-%) on TiO ₂	1-phenylacetone	61	[41]
8	propionic, benzoic	65:18:17	400	0.88	Na ₂ O (2.5 wt.-%) on TiO ₂	propiophenone	99	[39]
9	propionic, benzoic	53:32:15	470–510	0.4–1.0	CaO (3.87 wt.-%) on Al ₂ O ₃	propiophenone	98	[43]
10	propionic, benzoic	72:24:3	430	0.36	ZrO ₂ (10 wt.-%) on TiO ₂ or ThO ₂ (10 wt.-%) on TiO ₂	propiophenone	90	[41]
11	propionic, benzoic		380	batch	Cr oxide (ca. 5 wt.-%) on ZrO ₂	propiophenone	77 ^[e]	[44]

[a] Weight hourly space velocity. [b] The first two components are the two carboxylic acids and the third is water; normalized to 100. [c] Other rare earth metal oxides have been tested and give similar results. [d] At 60% conversion of pivalic acid. [e] At 79% conversion of benzoic acid.

possibility is available for 1-phenyl-1-propanone, which is also an intermediate used for preparing pharmaceuticals, ketonic decarboxylation is a real alternative that avoids the use of the acid chloride together with an equivalent amount of aluminium trichloride.^[35] The conditions for ketonic decarboxylation have been optimised and propiophenone can be obtained quantitatively with respect to the benzoic acid (Table 4, entries 8–11). Again, the catalysts employed in most of these cases were basic metal oxides on an anatase or an alumina support.

Cyclopentanone, as mentioned earlier, is also a commercially important compound that can be produced by ketonic decarboxylation. Two decisive factors result in this synthetic strategy, rather than cyclopentene oxidation, becoming the industrially preferred process. First, the substrate is a dicarboxylic acid, adipic acid, that has a much higher boiling point (ca. 330 °C) than does cyclopentanone (131 °C). Consequently, the product can be distilled easily from the reaction mixture. Secondly, the substrate, adipic acid, is a bulk product and, therefore, it is cheap and readily available.

The favourable boiling points allow the use of a different production process, rather than the common continuous reactor employed in the majority of ketonic decarboxylations of other substrates. It was realized very early on that cyclopentanone can be obtained by slow distillation of adipic acid or after thermal decomposition of its barium or calcium salts (Table 5, entries 1–3).^[7,8] Later, as discussed above in the section on the mechanism, the reaction was conducted in the presence of catalytic amounts of base. It was demonstrated that the strength of the base has no crucial influence on the reaction rate, but the amount does. Thus, no difference is observed when performing the reaction using either sodium hydroxide or sodium carbonate as base.^[45] Consequently, promoters for the ketonic decarboxylation of adipic acid include many kinds of bases, such as the strong potassium fluoride (Table 5, entry 9), hydroxides of alkali and alkali earth metals (entries 4–6 and 10), sodium phosphate (entry 11), and very weak carbonates (entry 12). Generally, cyclopentanone is obtained in 80–90% yield.

Similar yields are achieved when the reaction is performed in the modern form of the ketonic decarboxylation, i.e., placing a solid catalyst in a continuous reactor. For instance, yields of 87 and 88% were observed when using barium oxide or phosphate-impregnated silica catalysts (Table 6, entries 1 and 2). Interestingly, in the continuous reactor, the diethyl ester is the preferred substrate derivative over the free acid. This phenomenon may be due to its lower boiling point (245 °C vs. ca. 330 °C) and, therefore, easier evaporation. As a consequence, the reaction temperature could be lowered to 270 °C and cyclopentanone was obtained in 77% yield when using a potassium-oxide-on-anatase catalyst (Table 6, entry 3). However, the common catalysts applicable for monocarboxylic acids were not successful in all cases when using the ester substrates. In particular, ThO₂ and MnO₂ on alumina resulted in low selectivities (42 and 62%, respectively; Table 6, entries 5 and 9).

Table 5. Formation of cyclopentanone through ketonic decarboxylation and distillation from a batch reactor

Entry	Substrate derivative	T [°C]	Catalyst	Yield [%]	Select. [%]	Ref.
1	adipic acid		–	60		[7]
2	adipic acid	290–300	–	88–98		[8]
3	barium adipate	430	–	84		[8]
4	adipic acid		Ba(OH) ₂ (1.7 wt.-%)	87		[2]
5	adipic acid	285–295	Ba(OH) ₂ (5 wt.-%)	80		[10]
6	adipic acid	290–295	Ba(OH) ₂ (4 mol.-%)	>95		[4]
7	adipic acid	270–280	U(NO ₃) ₄ (4 mol.-%)	85		[4]
8	adipic acid	270–280	FeSO ₄ (4 mol.-%)	90		[4]
9	adipic acid	250–280	KF (5 mol.-%)	81		[13]
10	adipic acid	350	NaOH (10 mol.-%) ^[a]	84		[45]
11	adipic acid	250 ^[b]	Na ₂ PO ₄ (2 mol.-%)	71	90	[46]
12	adipic acid	250 ^[b]	Ca ₂ CO ₃ (2.6 mol.-%)	90	92	[47]
13	adipic acid	250 ^[b]	Na ₂ B ₄ O ₇ (1.4 mol.-%)	95	92	[47]
14	adipic acid	450	iron-containing graphite	90		[48]

[a] Similar yields were obtained when using the same amounts of other alkali and alkali earth metals. [b] Distillation from the reaction mixture using diethyl ether as solvent.

This cyclisation allows several alkyl substitutions in the substrate; the corresponding cyclopentanone is always obtained in yields of ca. 80% (Table 7). For instance, an 87% yield of 3-methylcyclopentanone was obtained from 3-methyladipic acid when using 5 mol.-% of Na₂CO₃ as the promoter (Table 7, entry 4). When starting with an enantiomerically pure compound, the enantiomeric excess is maintained in the product; thus, (*R*)-3-methyladipic acid is converted into (*R*)-3-methylcyclopentanone (entry 5). Adipic acid derivatives involving *tert*-butyl groups, as well as two or four methyl groups, are suitable substrates for the ketonic decarboxylation to the corresponding cyclopentanone derivatives (entries 6–10).

In contrast to the skeletal changes induced by alkyl substitution, elongation of the carbon chain of the dicarboxylic acid provides less-favourable results. Cyclohexanone may still be obtained in good yield (Table 8, entries 1–3), but its formation by ketonic decarboxylation is rarely performed for two reasons. Firstly, the substrate, heptanedioic acid, is not readily available; secondly, the product, cyclohexanone, can be obtained by a straightforward procedure from benzene through hydrogenation/oxidation processes.

The next homologue, cycloheptanone, may be synthesized by ketonic decarboxylation, but methods that work well for other substrates provide only moderate yields in this case. For instance, when reacting dimethyl octanedioate in the presence of alumina, cycloheptanone is obtained in a regular yield of 29% (Table 8, entry 6) as opposed to 69% in the case of cyclopentanone (Table 6, entry 8). At the

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Table 6. Formation of cyclopentanone through ketonic decarboxylation by passing the substrate over the solid catalyst bed placed in a continuous reactor

Entry	Substrate derivative	T [°C]	WHSV ^[a] [h ⁻¹]	Catalyst	Conv. [%]	Yield [%]	Select. [%]	Ref.
1	adipic acid ^[b]	345	0.27	BaO (5 wt.-%) on Al ₂ O ₃		88		[49]
2	adipic acid ^[c]	400	0.56	SiO ₂ (90 wt.-%) + NaH ₂ PO ₄ (10 wt.-%)		87		[49]
3	diethyl adipate	270	0.15	K ₂ O (2 wt.-%) on TiO ₂		77	94	[50]
4	diethyl adipate	300	0.1	La ₂ O ₃ (3% La) on ZrO ₂		82	84	[50]
5	diethyl adipate	325	2.0	ThO ₂ (20 wt.-%) on Al ₂ O ₃	43	18	42	[51]
6	monomethyl adipate	350	0.4	bauxite Fe-Al-Si-Ti		85		[52]
7	dimethyl adipate ^[d]	350	0.92	iron silicite (pentasil)	81	80	99	[53]
8	dimethyl adipate ^[e]	350	0.5	gamma-alumina	77	69	89	[54]
9	diethyl adipate	375	2.0	MnO ₂ (20 wt.-%) on Al ₂ O ₃	53	33	62	[51]
10	mixture monomethyl and dimethyl adipate	380	[f]	zeolite + 15 wt.-% Fe ₂ O ₃	60	59	98	[55]
11	mixture monomethyl and dimethyl adipate	400	[f]	clinoptilolite + 15 wt.-% MnO ₂ + 1.7% Cu	55	53	96	[56]

[a] Weight hourly space velocity. [b] Together with 75 wt.-% of water. [c] Alternatively, together with 82 wt.-% of water. [d] Together with 100 wt.-% of water. [e] Together with 22 wt.-% of water. [f] WHSV not reported.

Table 7. Ketonic decarboxylation with distillation of the substituted cyclopentanones obtained from the corresponding adipic acid derivatives

Entry	Substituents	T [°C]	Catalyst	Yield [%]	Ref.
1	3-methyl	450	iron-containing graphite	80	[48]
2	3-methyl	290–305	–	77	[4]
3	3-methyl	270–280	Zn dust (1%)	81	[4]
4	3-methyl	350	Na ₂ CO ₃ (5 mol.-%)	87	[45]
5	(R)-3-methyl	350	Na ₂ CO ₃ (5 mol.-%)	72	[45]
6	3- <i>tert</i> -butyl	350	Na ₂ CO ₃ (5 mol.-%)	83	[45]
7	2,2-dimethyl	225 ^[a]	Na ₃ PO ₄ (23 mol.-%)	77	[46]
8	2,2-dimethyl	225 ^[a]	Na ₂ B ₄ O ₇ (19 mol.-%)	80	[47]
9	2,2,5,5-tetramethyl	320–340	KF anhydrous (45 mol.-%)	52	[15]
10	2,2,5,5-tetramethyl	320–330	BaO (15 mol.-%)	72	[15]

[a] Distilled from the reaction mixture using diphenyl ether as solvent.

same time, the selectivity decreases from 89%, observed for the formation of cyclopentanone (Table 6, entry 8), to 50% when dimethyl octanedioate is converted into cycloheptanone (Table 8, entry 6).

Cyclic ketones having a nine-membered ring of carbon atoms or more are obtained in less than 5% yield – often only in traces (0.1–0.2%).^[57] There seems to be a clear trend: in the cases of cyclopentanone and cyclohexanone, ring formation is favoured. Cycloheptanone may be obtained by ketonic decarboxylation, but the ring closure to larger rings seems to be disfavoured. When elongating the carbon atom chain of the diacid, the reaction partner, the second carboxylic acid group, is positioned further away and the number of degrees of freedom increases. Consequently, the intermolecular version of the ketonic decarboxylation may compete efficiently.

Symmetrical linear long-chain ketones, the so-called fatty ketones, are obtained by ketonic decarboxylation of fatty acids. It has been demonstrated that this chemical reaction occurred in unglazed archaeological pottery thousands of years ago.^[58] Isotopic and structural analyses of the fatty acids, which always co-occur with the ketones, suggest that a precursor–product relationship exists. Fatty ketones have many applications, e.g., as fabric softeners, corrosion inhibitors, and flotation aids.^[60] They are the main components of water-in-oil emulsifiers for skin creams and lotions. After quaternisation or sulfonation they may be transformed into surfactants.^[60]

Table 9 lists several preparations for fatty ketones. Again, the same procedures as described above were applied for these ketonic decarboxylations, i.e., thermal decomposition of metal salts (older procedures are not included here), distillation of the free acid in the presence of catalytic amounts of an inorganic promoter, and the passage of vapours of the free acid or the methyl ester over a solid catalyst. An optimised distillation procedure is the one for the production of stearone using magnesium oxide as promoter (Table 9, entry 8).^[65] Stearic acid (3.8 mol) was treated for 2 h with magnesium oxide (2 mol) and then the resulting ketone was distilled under reduced pressure. Stearic acid (3.2 mol) was added to the residue and then the distillation was continued. The yield (70%) was maintained over 10 consecutive cycles. As an additional advantage, the fatty ketones obtained in this manner are almost colourless and can be employed directly in consumer goods without bleaching.

Because of the minor changes in material characteristics of the product when varying the number of carbon atoms of the linear chain, the fatty ketones can be applied as mixtures of ketones that have different chain lengths. For the production of these mixtures, natural fatty acid sources can be used without separation of their single components. For example, rape oil can be transformed into the methyl esters of its corresponding fatty acids by transesterification and

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Table 8. Transformation of heptanedioic acid and octanedioic acid derivatives into cyclohexanone and cycloheptanone, respectively, through ketonic decarboxylation

Entry	Substrate	T [°C]	WHSV ^[a] [h ⁻¹]	Catalyst	Product	Conv. [%]	Yield [%]	Select. [%]	Ref.
1	dimethyl heptanedioate/water (57:43 wt.-%)	345	0.28	Al ₂ O ₃	cyclohexanone	88	85	96	[54]
2	dimethyl heptanedioate/methanol/ water (79, 13, 8 wt.-%)	400	1.0	Li ₂ O (13.5 wt.-%) on MgO	cyclohexanone	70	70	100	[54]
3	heptanedioic acid	450	dist.	iron-containing graphite	cyclohexanone		80		[48]
4	dimethyl octanedioate/methanol/ water	440	[b]	ZnO (12 wt.-%) y?oas [q]?>on Al ₂ O ₃	cycloheptanone	65	49	76	[58]
5	dimethyl octanedioate/methanol/ water (71:23:6 wt.-%)	350	1.0	Cs ₂ O (18 wt.-%) on SiO ₂	cycloheptanone	46	27	59	[54]
6	dimethyl octanedioate/water (57:43 wt.-%)	345	0.28	Al ₂ O ₃	cycloheptanone	58	29	50	[54]
7	octanedioic acid	450	dist.	iron-containing graphite	cycloheptanone		17		[48]

[a] Weight hourly space velocity, [b] WHSV not reported.

Table 9. Transformation of fatty acids into fatty ketones through ketonic decarboxylation

Entry	Substrate	T [°C]	Reaction conditions	Catalyst	Yield [%]	Ref.
1	octanoic acid	420	[a]	MgO	76[b]	[61]
2	octanoic acid	398	WHSV = 1.2 h ⁻¹	Al-/Ti-oxide	88	[11]
3	nonanoic acid	399	WHSV = 1.55 h ⁻¹	ZrO ₂	70	[11]
4	decanoic acid	420	WHSV = 2.0 h ⁻¹	ZrO ₂	91	[11]
5	methyl dodecanoate	400	WHSV = 1.0 h ⁻¹	Sn-Ce-Rh-O	62[c]	[62]
6	dodecanoic acid	380	distillation	bauxite Fe-Al-Si-Ti	89	[52,63]
7	dodecanoic acid	330	[a]	MnO ₂ on pumice	95	[64]
8	octadecanoic acid	340	semicont. distillation	MgO	70	[65]
9	octadecanoic acid	360	[a]	MnO ₂ on pumice	95	[64]
10	octadecanoic acid/hexadecanoic acid (90:10)	380	distillation	bauxite Fe-Al-Si-Ti	82[d]	[52,63]
11	methyl esters from rape oil	385	WHSV = 1.5 h ⁻¹	Sn-Ce-Rh-O	60[d,e]	[66]
12	methyl esters from rape oil	390	WHSV = 1.0 h ⁻¹	Fe-Si-Cr-K-O	63[d,f]	[67]

[a] Continuous reactor; weight hourly space velocity (WHSV) not reported. [b] At a conversion of 82%. [c] Hydrocarbons were detected at 22%. [d] Mixture of ketones. [e] Hydrocarbons were detected at 13%. [f] Hydrocarbons were detected at 12%.

then treated at 385–390 °C in a continuous reaction using metal oxide catalysts (Table 9, entries 11 and 12). More than 60% of the crude product consists of fatty ketones.

A crucial point for the conversion of fatty acids into fatty ketones is the reaction temperature and the contact or reaction time. Long alkyl chains are very prone to cracking reactions. Methyl ketones, alkanes, and alkenes are the primary products that may be degraded further. The elevated temperatures probably cause these side reactions as a result of the high boiling points of the acids and the product ketones (see also the section describing the mechanism).

Future Perspectives

Ketonic decarboxylation is a very old reaction, but not an old-fashioned one. A synthetic reaction that requires only base catalysis for carbon–carbon bond formation meets the modern demands of green chemistry perfectly. The by-products – carbon dioxide and water – are low-polluting compounds. The co-factors, the exploitation of the

employed mass, range from 58% for the transformation of small molecules (e.g., propionic acid into 3-pentanone) to an excellent 89% for the conversion of stearic acid into stearone.

The field of applications of the ketonic decarboxylation will be similar in the future. Small symmetrical ketones may be produced by this reaction, including cyclic ones. In particular cases it may be an interesting solution for the synthesis of unsymmetrical ketones. Growth should be expected for the application of this reaction to fatty ketone production because this process is an elegant means for transforming fatty waste residues into commercially valuable products.

The relatively high reaction temperature required for this reaction is often the most serious problem when considering industrial applications. The design of bifunctional catalysts that involving basic sites together with other sites that are able to activate the second reaction partner may lower the temperature. Furthermore, ketonic decarboxylation remains a challenge for theoretical chemists to determine and confirm the reaction mechanism.

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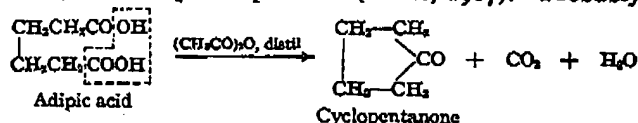
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RING FORMATION AND STABILITY

Cyclic Ketones. — Pyrolysis of the barium salt of adipic acid (p. 196) affords cyclopentanone in 80% yield, and cyclohexanone is produced in high yield from pimelic acid by the same method. Five- and six-membered cyclic ketones are produced so readily that acids of the adipic and pimelic types often can be converted into the ketones by simply heating the dibasic acid with acetic anhydride and distilling the excess reagent and the product, if it is volatile, at atmospheric pressure (Blanc, 1907). Probably the acid



is converted first into the polymeric anhydride, which then suffers pyrolysis rather than the depolymerization to the monomer observed when distillation is conducted in vacuum at a lower temperature, for pyrolysis of such polymers at atmospheric pressure affords ketones. Blanc observed that acids of the glutaric type, when submitted to the same process of distillation with acetic anhydride, are converted into anhydrides and not into cyclobutanone derivatives, and proposed this reaction as a diagnostic test for distinguishing between dibasic acids having a chain of five carbon atoms



(HOOC·C·C·C·COOH) and those having six or more carbon atoms in the chains (Blanc rule). Although the generalization accurately describes the behavior of the majority of acids, exceptions have been encountered in the case of certain highly substituted compounds of the adipic acid type that yield anhydrides rather than ketones.

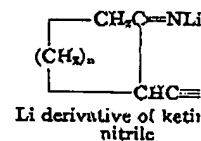
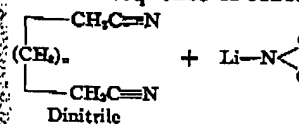
Synthesis of large-ring ketones by pyrolysis of metal salts of the corresponding acids is usually accomplished by heating the acid with the metal oxide. Calcium oxide appears preferable for the lower members of the series and thorium or cerium oxide better for the higher members. Ruzicka noted an interesting relationship between yield and ring size. The 5- and 6-ring ketones are obtainable in high yield, the yield of the 7-ketone is moderate and that of the 8-ketone fair (20%), but the ketones in the range C₉-C₁₃ are obtained under optimum conditions in yields of not more than 0.5%. From C₁₃ on, however, the yields improve and reach a secondary maximum of about 5% for the C₁₅-ketone, and then fall off to a level of about 2%. Ruzicka's discovery of the existence of large-ring ketones as the active principles of valuable perfumes, coupled with the observation that the pyrolytic method found applicable to the synthesis of such compounds gives at best yields of the order of 5%, presented a challenge for the development of an improved technique that was not slow in forthcoming. Ziegler in 1933 applied to the problem a principle that had appeared in the

literature (Ruggli,¹⁷ 1912) obstacle to formation of competing reaction of polymerization a function group A of surrounding molecule, and hence poly



conditions of the reaction opportunity for intramolecular objective consists merely If each molecule is sufficiently remote from others of its diminished and cyclization with any other monomol dependent of the concentration dilute solution as in a reaction, which is bimolecular by operating at high dilution

For utilization of the ring ketones it was necessary being conducted in a homogeneous solution, and Ziegler worked reaction meeting this requirement, and a condensing ester found in the ether-soluble. The full sequence of reaction

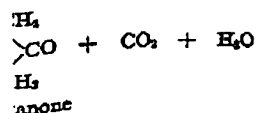


By virtue of the active group, the dinitrile is converted cyclization, pictured in the

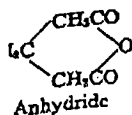
¹⁷ Paul Ruggli, 1884-1945; b. Basel; *Helv. Chim. Acta* 29, 796 (1946).

STABILITY

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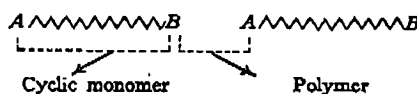
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CYCLIC KETONES

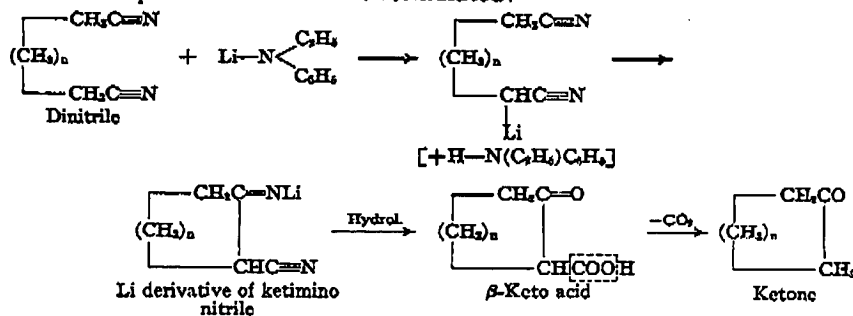
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literature (Ruggli,¹⁷ 1912) but had received little attention. The chief obstacle to formation of large-ring compounds is interference from the competing reaction of polymerization. Under ordinary conditions of experimentation a functional group B collides many more times with the group A of surrounding molecules than with that present in the same molecule, and hence polymerization predominates. Any variation in the



conditions of the reaction that will suppress polymerization must increase opportunity for intramolecular cyclization, and a means of achieving this objective consists merely in conducting the reaction at high dilution. If each molecule is surrounded largely by solvent molecules and is relatively remote from others of its kind, opportunity for intermolecular collisions is diminished and cyclization given a chance to proceed, even if slowly. As with any other monomolecular reaction, the rate of cyclization is independent of the concentration, and the reaction is just as rapid in a very dilute solution as in a concentrated one, whereas the velocity of polymerization, which is bimolecular in the initial phase, can be decreased enormously by operating at high dilution.

For utilization of the dilution principle in the preparation of large-ring ketones it was necessary to employ a cyclization reaction capable of being conducted in a homogeneous liquid phase with all the reactants in solution, and Ziegler worked out a suitable adaptation of the Dieckmann reaction meeting this requirement. A dinitrile was used in place of a diester, and a condensing agent to replace sodium or sodium ethoxide was found in the ether-soluble compound lithium ethylanilide, $\text{LiN}(\text{C}_2\text{H}_5)\text{C}_6\text{H}_5$. The full sequence of reactions is formulated:



By virtue of the activated position adjacent to the unsaturated nitrile group, the dinitrile is converted into a lithium derivative, which undergoes cyclization, pictured in the formulas as addition of the C-lithium to the

¹⁷ Paul Ruggli, 1884-1945; b. Montevideo (German parentage); Ph.D. Leipzig (Hantzsch); Basel; *Helv. Chim. Acta* 29, 706 (1946)